REMARKS

The Applicant has submitted, by separate letter, a Request for Continued Examination, a petition for a one month extension of time and an information disclosure statement.

Applicants have canceled claims 1-18 and have added new claims 19-52.

Reconsideration of the Application is requested.

Status of Application

Claims 19-52 are pending in the application.

Claims 1-18 are canceled without prejudice.

New claims 19-52 are added.

New claims 19-52 are supported throughout the specification. For the convenience of the Examiner, some of these claims are recited below with examples of textual support for various terms indicated in parentheses after the term.

Claim 19;

New claim 19 finds support in **original claim 11** and in the specification as indicated, for example, below;

An axon sprouting stimulation kit comprising

- a first container means comprising a first fibrin matrix (**original claim 4**) forming element,
- a second container means comprising a second fibrin matrix forming element,
- a mixing means (**page 18, line 1 and Figure 9**) for intermingling (**page 15, line 1**) said first and second fibrin matrix forming elements into a therapeutically acceptable fibrin matrix, and;
- a delivery means (**original claim 2**),

wherein at least one of said first and second container means further comprises a matrix-releasable (**page 17, lines 9-10**) therapeutically active agent selected from the group consisting of C3, Y-27632, Y-30141 (**page 8, line 8**) for facilitating axon sprouting at a nerve lesion site.

Claim 20;

New claim 20 finds support in **original claim 13** and in the specification as indicated, for

example, below;

The axon sprouting stimulation kit of claim 19, wherein C3 is selected from the group consisting of ADP-ribosyl transferase C3 derived from Clostridium botulinum, a C3 polypeptide having an insertion in one or more amino acids (**page 23, line 14**) and retaining ADP-ribosylation activity (**page 6, line 7, page 22, line 24**), a C3 polypeptide having a substitution in one or more amino acids (**page 23, line 14**) and retaining ADP-ribosylation activity, a C3 fragment retaining ADP-ribosylation activity and a recombinant C3 retaining ADP-ribosylation activity.

Claim 21;

The axon sprouting stimulation kit of claim 19, wherein one of said first or second fibrin matrix forming element is fibrinogen (**page 34, lines 5-12**) and the other of said first and second fibrin matrix forming element is a component for cleaving fibrinogen (**page 29, lines 19-22**).

Claim 22;

The axon sprouting stimulation kit of claim 19, wherein one of said first or second fibrin matrix forming element is fibrinogen (**page 34, lines 5-12**) and the other of said first or second fibrin matrix forming element is thrombin (**page 34, lines 5-12**) and wherein at least one of said first and second container means comprises calcium chloride (**page 10, line 14-15, page 29, line 19**).

Claim 23;

The axon sprouting stimulation kit of claim 19, further comprising, in one of said container means, a factor for catalyzing the cross-linkage of fibrin (**page 29, line 20 and 29**).

Claim 24;

The axon sprouting stimulation kit of claim 23, wherein said factor is selected from the group consisting of Factor XIII and Factor XIIIa (**page 29, line 20 and 27-29**).

Claim 25;

The axon sprouting stimulation kit of claim 19, further comprising a protease inhibitor (**page 18, line 6**).

Claim 26;

The axon sprouting stimulation kit of claim 19, further comprising fibronectin in one of

said container means (**page 29, line 20 and 30**).

Claim 27;

The axon sprouting stimulation kit of claim 19, further comprising, in one of said container means, an inhibitor selected from the group consisting of a plasminogen activator inhibitor and a plasmin inhibitor (**page 29, line 20, page 30, line 2**).

Claim 28;

The axon sprouting stimulation kit of claim 27, wherein said plasmin inhibitor is aprotinin (**page 30, line 3**).

Claim 29;

The axon sprouting stimulation kit of claim 19, further comprising a polysaccharide in one of said container means (**page 29, line 20, page 30, line 5**).

Claim 30;

The axon sprouting stimulation kit of claim 29, further comprising an inhibitor of polysaccharide degradation in one of said container means (**page 29, line 20, page 30, lines 5-7**).

Claim 31;

The axon sprouting stimulation kit of claim 29, wherein said polysaccharide is hyaluronic acid (**page 30, line 5**).

Claim 32;

The axon sprouting stimulation kit of claim 31, further comprising an inhibitor of hyaluronic acid degradation in one of said container means (**page 30, line 5-7**).

Claim 33;

The axon sprouting stimulation kit of claim 32, wherein the inhibitor of hyaluronic acid degradation is a hyaluronidase inhibitor (**page 30, line 5-7**).

Claim 34;

New claim 34 finds support in **original claim 16** and as indicated, for example, below;

An axon sprouting stimulation kit comprising

- a first container means comprising a first fibrin matrix (**original claim 4**) forming

element,

- a second container means comprising a second fibrin matrix forming element,

-a third container means comprising a therapeutically active agent selected from the group consisting of C3, Y-27632 and Y-30141 (**page 8, line 8**) for facilitating axon sprouting at said lesion site,

- a mixing means (**page 18, line 1 and Figure 9**) for intermingling the content (**page 15, line 1, page 18, line 4**) of said first, second and third container to form a therapeutically acceptable fibrin matrix containing a therapeutically active agent, and;

- a delivery means (**original claim 2**),,

wherein said therapeutically active agent is releasable from said therapeutically acceptable fibrin matrix into an adjacent external environment.

Claim 35; as defined for claim 20,

Claim 36; as defined for claim 21,

Claim 37; as defined for claim 22,

Claim 38;

New claim 38 finds support in **original claim 14** and in the specification as indicated, for example, below;

A biocompatible composition for facilitating axon sprouting, said composition comprising: (i) a therapeutically active agent selected from the group consisting of C3, Y-30141 (**page 8, line 8**) and Y-27632 for facilitating axon sprouting, and (ii) a fibrin matrix forming element (**original claim 4**).

Claim 39; original claim 14 and as defined for claim 21,

Claim 40; page 29, line 19,

Claim 41; as defined for claim 20,

Claim 42;

A kit for forming, in vivo at a nerve lesion site (**page 12, line 3; page 13, line 28**; **page 14, line 3, line 28**), a therapeutically acceptable fibrin matrix (**page 15, line 3**)

containing a releasable (**page 13, line 28**) therapeutic Rho antagonist agent (**page 21, line 28-29**) which elicits axon sprouting (**page 38, line 10**),

the therapeutic Rho antagonist agent selected from the group consisting of

Y-27632, (**page 7, line 18**)

Y-30141, (**page 8, line 8**)

C3 protein from Clostridium botulinum (**page 22, line 22**),

recombinant C3 proteins that retain ADP-ribosylation activity (**page 22, line 25**), and

truncation protein fragments of C3 retaining ADP-ribosylation activity to inactivate Rho GTPase (**page 23, line 11 and page 23, line 15-16 and page 22, lines 22-26**), wherein the truncation of one or more amino acids may originate from the amino terminus of the C3 protein, from the carboxy terminus of the C3 protein, or from the interior of the C3 protein (**page 23, line 10-16**),

the kit comprising:

a first solution comprising fibrinogen in a first container, (**page 34, line 5-8**)

a second solution comprising thrombin and calcium chloride in a second container, (**page 34, line 10-12**)

wherein at least one of said first solution and said second solution further comprises said therapeutic Rho antagonist agent, (e.**g., page 35, Examples 2 and 3**)

a means for mixing said first solution and said second solution (**page 18, line 1**) to form an activated solution of polymerizable fibrin (**page 14, line 10**) containing said therapeutic Rho antagonist agent which elicits axon sprouting; and

a means for application of said activated solution to said lesion site (**page 45, line 29**),

wherein polymerization of said polymerizable fibrin occurs at the lesion site within about 10 seconds (**page 38, line 3**) after said application, and

wherein said therapeutic Rho antagonist agent is releasable from said matrix into the adjacent external environment (**page 13, line 28-29; page 14, line 3-4**).

Claim 43;

The kit of claim 42, wherein the first container further comprises a component selected from the group consisting of Factor XIII and aprotinin. (**page 18, line 3; page 21, line 28-29; page 30, line 3**)

Claim 44;

The kit of claim 42, wherein the first solution comprises fibrinogen at 75 mg/ml, glycine buffer comprising 2 mg/ml of sodium chloride (NaCl) and 4 mg/ml of trisodium citrate and 15 mg/ml of glycine, and aprotinin at 3000 KIU/ml. (**page 34, Example 1**)

Claim 45;

The kit of claim 42, wherein the second solution comprises 500 IU/ml thrombin, 2.4 mg/ml glycine, 8 mg/ml sodium chloride, and 40 umol/ml calcium chloride. (**page 34, Example 1**)

Claim 46;

The kit of claim 42, wherein the application is by means of a syringe and needle. (**page 15, line 16; page 31, line 5-6; page 32, line 13**)

Claim 47;

The kit of claim 42, wherein the means for mixing is a syringe selected from the group consisting of a single syringe (**page 31, line 6**), a syringe having a mixing compartment (**page 31, line 10**), two syringes attached by a three-way stopcock, (**page 31, line 14**), and two syringes having a common plunger (**page 31, line 17-18**).

Claim 48;

The kit of claim 42, wherein the therapeutic Rho antagonist agent is present as a substantially uniform dispersion (**page 12, line 21**) in the activated solution (**page 12, line 21-23**).

Claim 49;

The kit of claim 42, wherein the therapeutic Rho antagonist agent is a C3 protein present as a dose of about 3 grams per 60 kilogram person (**page 13, line 1**).

Claim 50;

The kit of claim 42, wherein the therapeutic Rho antagonist agent is a C3 protein present at a concentration of 25 to 50 micrograms per milliliter. (**page 28, line18**)

Claim 51;

The kit of claim 42, wherein the therapeutic Rho antagonist agent is a C3 protein present at a concentration of 1/3 milligrams per milliliter. (**page 34, lines 14-18**).

Claim 52;

The kit of claim 42, wherein the lesion site is in an injured spinal cord. (**page 18, line 32 to page 19, line 1**)

New claim 19 to 52 refers to "fibrin matrix forming elements" or "fibrin matrix" and to "therapeutically active agent" or "therapeutic Rho antagonist" which are "selected from the group consisting of C3, Y-27632 and Y-30141".

The Applicant respectfully submits that "fibrin matrix" or "fibrin matrix forming element" and "therapeutically active agent" or "therapeutic Rho antagonist" selected from the group consisting of C3, Y-27632 and Y-30141" are enabled in the Example section such as, for example, page 33, line 28 to page 35, line 25 and from page 36, line 30 to page 38, line 14. The structure of some exemplary embodiments of the active agent is also described at page 6, line 31 to page 9, line 16 and at page 43, lines 6-10.

More particularly, at page 34, line 5 to page 35, line 4, Applicants have demonstrated how to prepare kits and compositions of the present invention.

In light of the above, the Applicant respectfully submits that the specification provides written description and is enabling for a kit and a composition for facilitating axon sprouting comprising "fibrin matrix forming elements" or "fibrin matrix" and "therapeutically active agent" or "therapeutic Rho antagonist" which are "selected from the group consisting of C3, Y-27632 and Y-30141".

Applicants point out that the phrase "C3 analogue" does not appear in the language of new claims 19-52, and the "active agent" or "Rho antagonists" claimed are finite and well defined.

The Applicant would like to bring to the Examiner's attention that the active site of C3 that is responsible for ADP-ribosylation activity to inactivate Rho GTPase

is well known in the art (see for example Saito et al. FEBS Letters, 371:105-109, 1995). In addition, the sequence of C3, from which the fragments or truncations are derived, is described in the specification. The locations of allowable truncation of C3 are described together with the requirement that the truncation fragments "will have the biological property of C3 that is capable of inactivation of Rho GTPases" (see specification page 23, line 15-16). Thus, the specification refers to a set consisting of a limited number of well defined C3 truncation, fragments, insertion and substitution of peptide molecules having retained ADP-ribosylation activity. The specification also describes how "active agent" or "Rho antagonist" activity can be experimentally determined in at least one assay (see for example page 15, line 19 to page 16, line 17; and page 28, line 1 to page 29, line 10). Thus, given the limited number of possible C3 truncation, fragments, insertion and substitution peptides having ADP-ribosylation activity, the known identity of the active site required for ADP-ribosylation in C3, and the method to determine the presence of Rho antagonist activity, a skilled artisan can identify the set of C3 truncation, fragment, substitution or insertion peptides referred to in the current application and know how to practice the invention from the teachings of the specification.

For the reasons outlined below, it is submitted that claims 19-52 are now in condition for allowance. An early allowance of these claims is respectfully requested.

The US Patent Office is hereby authorized to charge the amount of $ 340.00 to our **Deposit Account no. 02-3980** for excess claim fees.

The US Patent Office is hereby authorized to charge the amount of $ 790.00 to our **Deposit Account no. 02-3980** for the Request for Continued Examination.

If any further fees, **whatsoever**, with respect to the above mentioned application are required, the United States Patent Office is in any event hereby authorized to charge any necessary fees to our above Deposit Account.

Respectfully submitted,

Université de Montréal,

By

BROUILLETTE KOSIE PRINCE

Ronald S. Kosie
Reg. No. 28,814
1100 René-Lévesque Boulevard West
25th floor
Montréal, Québec, Canada
H3B 5C9

Telephone: (514) 397-6942
Fax: (514) 397-8515

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